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A phenomenological-based semi-physical model of the kidneys and its role in glucose metabolism

Laura Lema-Perez, Ph.D.[a,*], Carlos E. Builes-Montaño, M.D.[b], Hernan Alvarez, Ph.D.[a]

[a] *Universidad Nacional de Colombia, Facultad de Minas, Escuela de Procesos y Energía. Kalman research group, Cra 80 No 65-223, 050041, Medellín - Colombia*
[b] *Hospital Pablo Tobón Uribe, Calle 78b No 69 - 240, 050010, Medellín - Colombia. Universidad de Antioquia, Facultad de Medicina, Cra. 51d No 62-29, 050010, Medellín - Colombia*

Abstract

The kidneys play an important role in glucose homeostasis in three ways: Via endogenous glucose production from non-carbohydrate precursors (e.g. glutamine, lactate, alanine, glycerol) during both postprandial and post-absorptive states; via glucose filtration and reabsorption by the glomerulus and proximal tubule, respectively; and via glucose utilization and the elimination of its excess in the urine when glucose levels exceed $180 mg/dl$. The renal release of glucose into the circulation occurs mainly in the renal cortex and results from the glucose phosphorylating capacity of those renal cells, meaning that, cells in the renal cortex can form glucose-6-phosphate. Considering glucose filtration and reabsorption, the kidneys filtrate and reabsorb all circulating glucose, rendering the urine virtually glucose-free in a healthy person. Finally, the kidneys take up glucose from the circulation for energetic self-supply. Besides their role in glucose metabolism, the kidneys are the major site of insulin clearance from the systemic circulation, removing approximately 50% of peripheral insulin. In this regard, insulin clearance by kidneys occurs by degradation in the proximal tubule after being filtered in the glomerulus. All the aforementioned mechanisms affect the glucose concentration levels in the blood, preventing the parametrization of a mathematical model for patients with diabetes mellitus, in the implementation of an artificial pancreas. Aiming for a complete physiological model of the glucose homeostasis, a physiological submodel of the kidneys is presented in a way not described in the literature so far. This submodel is a phenomenological-based semi-physical model with a basic structure rooted in the conservation law and for which the parameters are interpretable. The model's results coincide well with the available clinical data reported for kidney functions associated with glucose and insulin.

Keywords: Physiological systems, kidneys, glucose metabolism, parameter interpretability, phenomenological-based semi-physical model (PBSM).

*Corresponding author
URL: `llemap@unal.edu.co` (Laura Lema-Perez, Ph.D.)

1. Introduction

Diabetes mellitus is a chronic disease caused by a disturbance in human body glucose homeostasis. Disequilibrium in glucose homeostasis is, among other disorders in the glucose-insulin dynamics, a widespread condition affecting many people around the world. Mathematical models can lead to a better understanding and control of the blood glucose levels [1, 2, 3, 4, 5]. Most of the studies are focused on the main organs involved in this regulatory system such as the pancreas and the liver. However, other organs participate in glucose homeostasis whose role has been disregarded in the literature so far. For example, the kidneys make a significant contribution to glucose metabolism and insulin metabolism for clearance. The kidneys act in three ways. First, kidneys produce and release glucose via gluconeogenesis. Second, kidneys consume glucose from the blood to carry out their basic metabolic functions. Third, kidneys filtrate glucose through the glomerulus and reabsorb glucose through renal tubules, allowing excess glucose to be eliminated via the urine.

The kidney may be perceived as two separate organs because the two main mechanisms in glucose metabolism occur in different parts: Glucose production occurs mainly in the renal cortex and glucose utilization takes place in the renal medulla. The kidneys also have highly specialized functional units, nephrons, composed of a glomerulus, surrounded by glomerular capillaries; that is, they are connected to a tubular portion transporting waste to be eliminated in the urine. Just like glucose, insulin is filtered by the glomerulus and partially reabsorbed in the proximal tubules [6]. Once the insulin is in the tubular lumen, it enters the proximal tubular cells by carrier-mediated endocytosis and is then transported into lysosomes, where it is metabolized into amino acids [7]. Approximately 40% of total renal insulin clearance occurs by extraction from the peritubular vessels [8], whereas 60% is due to glomerular filtration so, the rate of renal insulin clearance exceeds the glomerular filtration rate.

Existing mathematical models that represent the glucose-insulin system frequently include variables that cannot be directly measured [5]. These models are constructed based on experimental data taken from standard clinical tests that provide very little information on how to interpret the parameters of the model according to the physiological threshold where they could have meaning. These models do not consider relevant aspects that are crucial in explaining physiological phenomena or providing a clinical interpretation of the natural underlying system. Consequently, it is difficult to individualize the parameters of the models in a patient used to tune automatic systems of insulin dosage to regulate blood glucose levels. In the case of kidneys, a mathematical model describing the role of this organ in the glucose regulation cycle has not been proposed. The only aspect considered in the reported mathematical models is a parameter representing the glucose renal excretion in urine when a patient under a metabolic glucose-insulin disorder is considered [9, 10].

In the present work, a phenomenological-based semi-physical model (PBSM) of the relevant physiological aspects of the kidney's role in glucose homeostasis is developed. This model can be

coupled to another model of the whole glucose regulatory system in humans including those areas highlighted as potential targets for diabetes treatment. A mathematical model of the role of the kidneys in glucose metabolism will give further insights into a complete picture of the natural glucose regulation mechanism. Bearing the above in mind, a reliable and exhaustive model of glucose homeostasis could outperform the prediction ability of existing models in the literature, becoming a powerful tool for a model-based controller acting as the core of an artificial pancreas. The paper is organized as follows. In Section 2, a summary of the main aspects of the phenomenological-based semi-physical model family is presented. In Section 3, the procedure to construct PBSMs is applied to model the role of the kidneys in glucose homeostasis in the human body. In Section 4 the results of the model are discussed. Finally, concluding remarks are provided in Section 5.

2. The process of PBSM construction

Modeling is a process aimed at representing the reality. However, reality is so complex that it can be represented in many ways, which explains the existence of various modelling methodologies [11, 12, 13, 14, 15, 16, 17]. A methodology to construct phenomenological-based semi-physical models, based on that proposed by Hangos and Cameron [13], is proposed by [18]. This methodology is an iterative procedure described in 10 steps [19], used here to develop a model of the role of the kidneys in the glucose metabolism. The procedure is clustered into three sections: Model pre-construction, model construction, and simulation of the computational model. Model pre-construction consists of process description, model aim, model hypothesis, level of detail, and definition of the process systems. Model construction includes the application of the conservation law, the determination of the model's basic structure, definition of the variables, structural parameters, and constants, and the determination of constitutive and assessment equations for the model. Finally, verification of the degrees of freedom is performed to construct the computational model, followed by model simulation.

A mathematical model is constructed to explain or represent a phenomenon. A phenomenon is described mathematically from its origins using of experimentation. However, different experimental scenarios can be tested with the model that represents the phenomenon without needing to repeat experiments or collect data, such a model is phenomenological. Hence, purely phenomenological models, i.e., first principles models, are based on the theories governing the phenomena of interest without the need for data. The phenomenological-based semi-physical models are a family of models that are built based on knowledge of the described phenomenon, but also using data to estimate parameters representing unknown phenomena affecting the real object. A PBSM has four properties that make it different from other types of models: i) Uniqueness of the model's basic structure due to balance equations, obtained by applying the conservation law, which is the same for each process family; ii) modularity, that is, the ability to expand from an initial model that considers only a part of the process to a model considering a larger layout; iii) the levels of

detail can be combined and modeling is possible on as small a scale as required; iv) parameter interpretability, i.e., most of the parameters of the model have a physical meaning within the process being modeled. The procedure to construct phenomenological-based semi-physical models is detailed in Section 3 applied to the kidney's role in glucose metabolism.

3. Construction of a PBSM describing the human kidney's role in glucose homeostasis

In this section, a PBSM of the role of the kidneys in glucose homeostasis in humans is developed. More specifically, this model represents the kidney as a whole, but through the functional unit of the kidney, the nephron. This follows the fact that each component of the nephron has a specific function in the physiology of the kidney. To obtain the results for the whole kidneys, the results for one nephron are multiplied by the 2 million of nephron that on average, make up both kidneys. The parameters of the mathematical model are interpretable, i.e., most of the parameters have a physical meaning from physiological knowledge of the kidneys. This fact is crucial when the model parameters need to be adjusted for a given patient.

3.1. Model pre-construction

3.1.1. Process description and model aim

The kidneys play an important role in glucose homeostasis. Similar to the liver, the kidney is the only organs able to perform gluconeogenesis from non-carbohydrate carbon substrates especially from glutamine, which is its favorite precursor in terms of affinity. The kidneys participate in the glucose regulatory cycle through three main mechanisms: 1) glomerular filtration and reabsorption of glucose, 2) endogenous glucose production from non-carbohydrate precursors, and 3) glucose utilization to be used in metabolic processes like the rest of the organs.

The glucose circulating in the blood reaches the renal artery and enters the kidney through the hilum. The hilum then converts into the afferent arterioles, which lead to the glomerular capillaries. Figure 1 represents the physiological processes of glucose in a nephron. The glomerular capillaries are covered by epithelial cells, and the whole glomerulus is enclosed by the Bowman's capsule [20]. There, all circulating glucose is filtered crossing the Bowman's capsule towards the proximal tubules located in the cortex of the kidney. The proximal tubules are the only part of the nephrons with appropriate enzymes used in gluconeogenesis [21]. Four substrates are largely responsible for endogenous glucose production in the kidneys ($\sim 90\%$ of the gluconeogenesis): Lactate, glutamine, glycerol, and alanine [21],[22]. All of these precursors are fully filtered by the glomerulus and almost completely metabolized in the proximal tubules [23, 24], following the same pathway as glucose. Previous research suggested that insulin is typically filtered at the glomerulus and then almost completely reabsorbed or degraded in the proximal tubule [25]. In contrast, glucagon has

little or no effect on renal gluconeogenesis [26, 27, 28].

Depending on the concentrations of glucose, insulin, and their precursors in the blood, a certain amount of glucose is also produced via gluconeogenesis in the proximal tubule in the renal cortex. This glucose production occurs via biochemical reactions of different substrates, as mentioned before, and stimulated by enzymes in the proximal tubule. The end products of the biochemical reactions are partially reabsorbed into the blood, glucose is transported using sodium glucose cotransporters (SGLTs) in the proximal convoluted tubules, and the fraction that is not reabsorbed continues to flow via the loop of Henle, until it reaches the renal collecting duct and is excreted in the urine [29]. The glucose reabsorbed from the proximal tubules by SGLTs cotransporters is then released into the circulation through the action of facilitative glucose transporters (GLUTs) located in the basolateral membrane of the epithelial cells lining the proximal tubules [30]. The distal ends of the capillaries of each glomerulus converge to form the efferent arteriole, which leads to a second capillary network, i.e., the peritubular capillaries, that surround the renal tubules. Here the glucose is reabsorbed into the blood. Simultaneously, cells in the renal medulla consume glucose both in the postabsorptive and the postprandial state [21]. Virtually all of the filtered glucose is subsequently reabsorbed into the proximal convoluted tubule via sodium-dependent glucose cotransporter (SGLT) proteins [21]. The peritubular capillaries merge together and exit the kidney as the renal vein, containing all the reabsorbed substances.

3.1.2. Model hypothesis and level of detail

The nephrons are specialized structures composed of different parts. Each specific part carries out a specific function affecting blood glucose concentrations, as previously described. Therefore, the renal tissue is modelled as multiple individual nephrons to obtain a macroscopic model of the kidney's role in the glucose homeostasis. The analogy proposed for representing an equivalent nephron to model the kidney's role in the glucose homeostasis is shown in Figure 2. The glomerulus and the end of the proximal tubule where re-absorption of substances occurs are represented as two continuous filters. The proximal tubule where renal gluconeogenesis occurs is represented as a continuous stirred-tank reactor (CSTR) despite it being a long circular duct. The plug flow reactor behavior, which would be a more realistic representation, is not used here given its complexity and its little contribution to additional model precision. Glucose consumption by the kidneys is evaluated as the energy dissipated $\dot{Q}$ assumed over the proximal tubule, even though it is consumed by the kidneys as a whole. The arrow representing heat ($\dot{Q}$) does not affect the enthalpy of any current. Therefore, an energy balance is not required because this energy representing the metabolic processes in the nephrons is directly computed using an assessment equation. This is represented as a parameter of glucose consumption in Section 3.2. The blood flowing in all vessels surrounding each nephron and the kidneys, i.e., the renal artery, the renal vein, the efferent and the afferent arterioles, and the peritubular capillaries, is represented as a perfectly stirred tank. This model

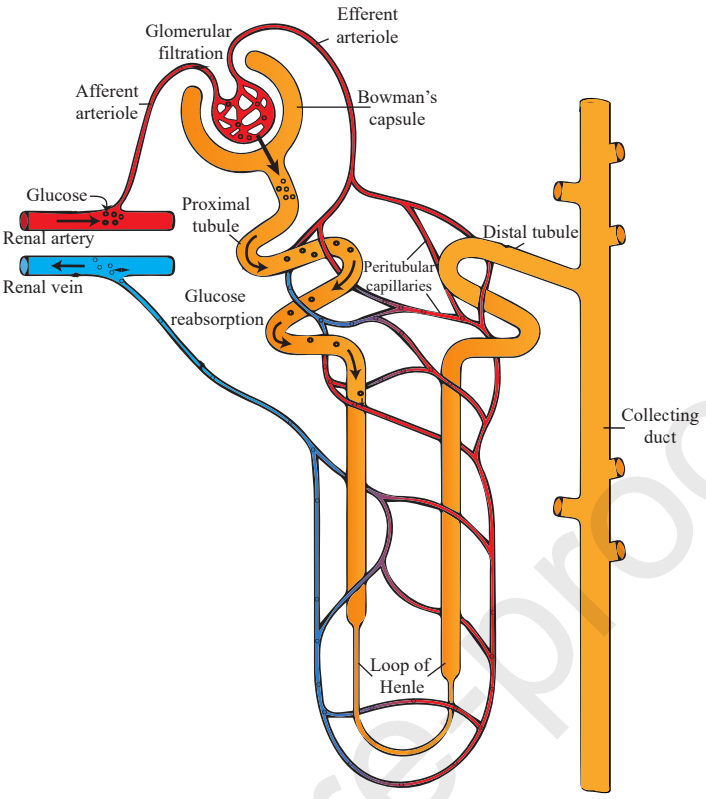

Figure 1: Representation of one nephron with respect to glucose homeostasis.

145 makes it possible to simulate how renal physiology affects the blood glucose concentrations when
146 exiting of the kidneys' blood circulation.

147

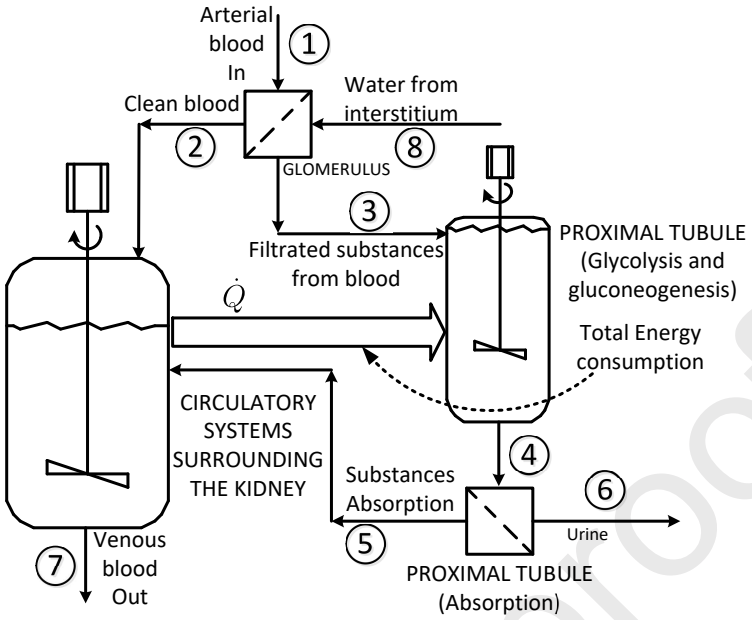

Figure 2: Proposed analogy of a nephron and its role in the glucose homeostasis. Glomerulus and the part of the proximal tubule where reabsorption of substances occurs are represented as a filter, the proximal tubule as a continuously stirred reactor, and the circulatory system as a continuously stirred tank. Total energy consumption $\dot{Q}$, even if not computed as an energy balance, is used here to represent the glucose uptake in the nephrons to carry out their metabolic processes.

Biochemical reactions occurring in the kidneys and involved in glucose homeostasis are detailed in Section 3.2. An important fact is that renal tissue is separated from blood both by the endothelium of capillaries and by the proximal tubule wall, which facilitates the assumed partition of the system and, consequently, the modeling hypothesis. The main variable of the modelled system is glucose dynamics, but insulin, water, and the substrates for renal gluconeogenesis: glutamine, lactate, alanine, and glycerol, are also analyzed because they also play a role in glucose production and consumption in the kidneys.

The following ones are complementary assumptions supporting this hypothesis: i) Although blood is mostly water (more than 90%) [31] and this water is completely filtered in the kidneys, the only water considered to be exchanged between the interstitium and the tubular lumen is that which is required for biochemical reactions. For the sake of simplicity, water in the blood is not considered in the model in order to avoid having to include it in several balances without adding information to the model. ii) Parameters $\dot{m}_3$ and $\dot{m}_4$ are equivalent to $\dot{n}_3$ and $\dot{n}_4$ but in mass units. The meaning of the parameters are reported in Section 3.1.3. iii) The total mass balance of the PS_{II} is assumed as the sum of the total moles of each component in the proximal tubule. iv) The term $r_{EGP,i}$ is assumed to be the total glucose production in the kidneys. v) The amount of precursor entering the tubule is exactly the amount needed to produce glucose. vi) All the water needed to form glucose and urine enters the lumen of the tubules from the glomeruli (stream 8).

166 *3.1.3. Process system definition*

167 A process system (PS) is a part of a modeled object, abstracted from the real process in the
168 form of a system using a specific criterion of partition over the modeled process or a part of it [32].
169 Accordingly, every PS can be regarded as a volume in which a change occurs in the properties of the
170 substances of interest. In the kidneys, four PSs are defined, as shown in Figure 3. The PS I (PS_I)
171 represents the glomerulus where blood is filtered and where all substances that can pass through
172 the three layers of Bowman's capsule reach the proximal tubule. Blood entering the glomerulus via
173 the renal artery is represented by stream 1, but continues to flow through the capillaries (stream
174 2) until it exits the kidneys via the renal vein (stream 7). The filtered substances travel through
175 stream 3 and enter into the proximal tubule where gluconeogenesis takes place. This part of the
176 proximal tubule is taken as PS II (PS_{II}). Blood surrounding the kidneys is represented as a per-
177 fectly stirred tank, considered as PS IV (PS_{IV}). Every biochemical reaction occurs in the first
178 part of the proximal tubule where glucose is produced. This glucose continues towards the second
179 filter via stream 4, making up the third process system, PS III (PS_{III}). The glucose and other
180 substances are reabsorbed into the blood by stream 5. The non-reabsorbed substances continue
181 through the tubule until they reach the collector duct to be eliminated later in urine (stream 6).
182 Finally, water needed for the reactions and to form urine, is assumed to come from the interstitial
183 space to the nephron via stream 8.

184

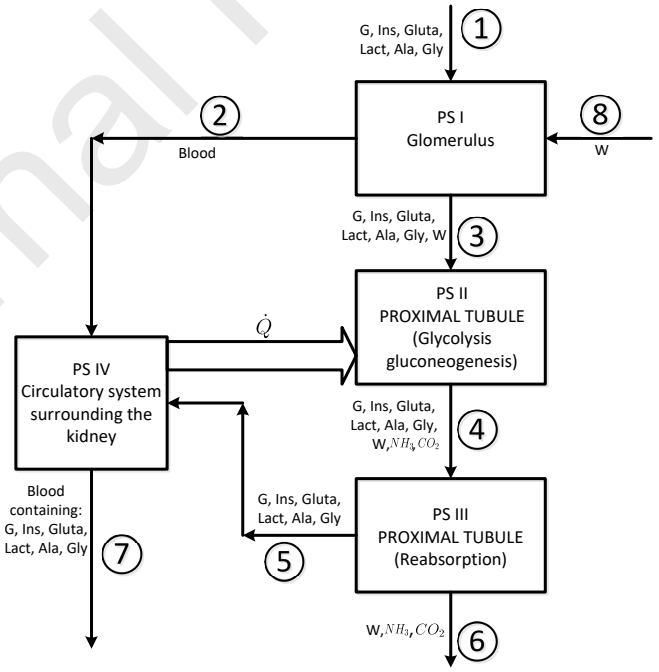

Figure 3: Block diagram of process systems taken for modelling the kidneys. Abbreviation for the chemical species flowing through each stream are specified by the corresponding arrow.

3.2. Construction of the mathematical model

3.2.1. Application of the conservation principle

Mass balances in molar units are applied to PS_{II} to facilitate the handling of biochemical reactions in the kidneys. In the other PSs, mass units are used. Both, the total mass balance and mass balance for each substance of interest are considered. The mathematical development of each PS is as follows.

3.2.2. PS_I - Glomerulus

As mentioned before, the glomerulus is considered a filter because its function of blood filtration across the capillary walls in the Bowman's capsule. All mass flows will be represented by $\dot{m}_k$, k being the number of the stream in accordance with Figure 3.

Total mass balance. The total mass balance of the PS_I is given by

$$\frac{dM_I}{dt} = \dot{m}_1 - \dot{m}_2 - \dot{m}_3 + \dot{m}_8 \tag{1}$$

where M_I is the total mass of substance contained into PS_I, $\dot{m}_1$ is the blood flow supply from an afferent arteriole of the renal arterial circulation received by the glomerulus. $\dot{m}_2$ represents the blood flow from the glomerular capillaries, and free of filtered substances, and that continues to flow towards the renal venule, which in turn enters a renal interlobular vein and then the renal vein. $\dot{m}_3$ is the filtered flow that has passed through the three-layered filtration unit and the Bowman's space to flow into the renal tubule. $\dot{m}_8$ represents the flow of water exchanged with the interstitial space to carry out the chemical reactions that take place in the renal tubules and the water to form urine. The water exchange between the tubules and the interstitial space is due to the sodium equilibrium. This sodium is not used in the biochemical reactions and therefore not considered in this model. $\frac{dM_I}{dt} = 0$ because there is no mass accumulation in the glomerulus. In this way, the total mass balance for PS_I is

$$\dot{m}_2 = \dot{m}_1 - \dot{m}_3 + \dot{m}_8 \tag{2}$$

with $\dot{m}_2$ being the unknown variable because $\dot{m}_1$ and $\dot{m}_8$ are operative parameters, and $\dot{m}_3$ is known thanks to reactive demand from PS_{II}.

Component mass balance. In PS_I, the mass balance component for glucose (G) is of particular interest, as it is directly related to the answer to the model question, i.e., the change in the mass fraction of glucose in the bloodstream due to the consumption and production of glucose in the kidneys. However, a mass balance is also performed for other components of interest such as insulin (Ins), water (W), and non-carbohydrate precursors such as glutamine (Gluta), lactate (Lac), alanine (Ala), and glycerol (Gly). Balance for glucagon is not performed because, as mentioned

earlier, glucagon does not play an important role in the kidneys [26, 27]. The component mass balance is written in generic form as

$$\frac{dM_{j,I}}{dt} = w_{j,1}\,\dot{m}_1 - w_{j,2}\,\dot{m}_2 - w_{j,3}\,\dot{m}_3 + w_{j,8}\,\dot{m}_8 \tag{3}$$

where $w_{j,k}$ is the mass fraction of component j in the stream k, with j : G, Ins, Gluta, Lac, Ala, Gly, and W. The term $w_{j,2} = 0$ because G, Ins, Gluta, Lac, Ala, and Gly are entirely filtered by the glomerulus and they cross the capillaries located within Bowman's capsule freely. Moreover, these substances enter the glomerulus from the bloodstream and not from the interstitial space, therefore $w_{j,8} = 0$ too except for water, which $w_{W,8} = 1$. Considering that no substances are accumulated in PS_I, $\frac{dM_{j,I}}{dt} = 0$, and considering perfect agitation for stream 3, it is possible to rewrite the mass balances, for a generic component in PS_I, as the following algebraic expression

$$w_{j,3} = \frac{w_{j,1}\,\dot{m}_1}{\dot{m}_3} \tag{4}$$

where $w_{j,3}$ is the mass fraction of component j (for $j \neq W$) filtered by the glomerulus and $w_{j,1}$ the mass fraction of component j reaching the glomerulus from the afferent arteriole.

When considering the mass balance for water, this substance enters the glomerulus by stream 8 and continues in stream 3, being $w_{W,1} = w_{W,2} = 0$ from Equation 3. There is no water accumulation in the glomerulus, so $\frac{dM_{W,I}}{dt} = 0$. Thus, the mass balance for water is

$$w_{W,3} = \frac{w_{W,8}\,\dot{m}_8}{\dot{m}_3} \tag{5}$$

3.2.3. PS_{II} - Proximal tubule where glycolysis and gluconeogenesis take place

The first part of the proximal tubule, called proximal convoluted tubule, where glycolysis and gluconeogenesis take place, is modelled as a continuous stirred tank reactor (CSTR). Endogenous production of glucose involves the formation of glucose-6-phosphate from the non-carbohydrate precursors lactate, glycerol, alanine, glutamine, and amino acids, with its subsequent hydrolysis by glucose-6-phosphatase to glucose. Therefore, these four precursors together with insulin and glucose are the substances of interest to be balance in this PS. As previously mentioned, in PS_{II}, molar units are used for balances to facilitate the handling of chemical reactions. All molar flows are presented by $\dot{n}_k$, k being the number of the stream as indicated in Figure 3.

Total mass balance. This balance for PS_{II} is written in a generic form as

$$\frac{dN_{II}}{dt} = \dot{n}_3 - \dot{n}_4 + \sum\sum(r_{EGP,i}\,\sigma_{j,i}) \tag{6}$$

where N_{II} is the total mass of substance, taken as kilo-mole, in PS_{II}. $\dot{n}_3$ is the molar flow, equivalent to $\dot{m}_3$ through units conversion, of the filtrate flowing from the Bowman's capsule to the proximal tubule. The products of chemical reactions continue to flow into the proximal straight tubule until they reach the loop of Henle. They are represented by $\dot{n}_4$. $r_{EGP,i}$ is the

reaction rate for endogenous glucose production by the kidneys. Subindex i represents the four chemical reactions, and j, the reaction products, glucose, water, NH_3, CO_2, insulin, and the four main precursors considered for the renal endogenous glucose production, $\sigma_{j,i}$ is the stoichiometric coefficient of each substance j in the balanced equation for reaction i. The sign of $\sigma_{j,i}$ is positive if the substance is a product and negative if it is a reactant. $\sigma_{j,i} = 0$ indicates that substance j does not react. This balance equation indicates that N_{II} changes due to the appearance or disappearance of particular substances when biochemical reactions take place. This is evaluated using the double sum (over i and j) at the end of the balance. The biochemical reactions of gluconeogenesis through non-carbohydrate precursors are as follows.

Reaction $i = 1$. Endogenous glucose production via glutamine is given by the following balanced stoichiometric equation [33]

$$\begin{aligned} Glutamine + 2NAD^+ + FAD^+ + ATP + 5H_2O \rightarrow \\ 2NH_3 + 2CO_2 + 2NADH^+ + 2H^+ + FADH_2 + ADP + Pi + 0.5Glucose \end{aligned} \tag{7}$$

Reaction $i = 2$. Endogenous glucose production via lactate. Lactate first becomes pyruvate and then pyruvate is synthesized into glucose [34]

$$L - Lactate + 2ATP + GDP + 3H_2O \rightarrow 0.5Glucose + 2ADP + GDP + 3Pi \tag{8}$$

Reaction $i = 3$. Endogenous glucose production via alanine. This reaction is similar to lactate reaction, but glucose production via alanine produces ammonia that is then eliminated in urine [34]

$$Alanine + 2ATP + GTP + 4H_2O \rightarrow 0.5Glucose + NH_3 + 2ADP + GDP + 3Pi \tag{9}$$

Reaction $i = 4$. Endogenous glucose production via glycerol. The metabolic pathway of glycerol is shorter than others and glycerol is perhaps the only precursor that is not first converted via pyruvate [35]

$$Glycerol + ATP + NAD^+ + H_2O \rightarrow 0.5Glucose + ADP + 0.5Pi + NADH^+ + H^+ \tag{10}$$

In this PS_{II}, j is used for the following substances, each one with a component balance in the biochemical reactions previously detailed: glucose (G), insulin (Ins), glutamine (Gluta), lactate (Lac), alanine (Ala), glycerol (Gly), water (W), ammonia (NH_3), and carbon dioxide (CO_2). Following the sign convention and from previous balanced stoichiometric equations, the signs of the reaction rates are positive for G, NH_3, and CO_2, and negative for Gluta, Lac, Ala, Gly, and W.

The total mass balance in *kmol* units is useful to follow the moles, but does not represent the operating conditions of the constant reactor volume. Therefore, this operational condition must be represented by stating a constitutive equation as the sum of the total moles of every component of interest as shown in Equation 11, detailed in Section 3.2.8 and in Table 3.

Component mass balance. In this PS, component mass balances are performed for G, Ins, Gluta, Lac, Ala, Gly, W, NH_3, and CO_2. Balances for glucagon are not performed given that as

mentioned earlier, cells in the renal cortex responsible for the gluconeogenesis have little phosphorylating capacity and, under normal conditions, they cannot significantly synthesize glycogen [22]. Therefore, glucagon has no glycogen to dephosphorylate in the kidneys, as this occurs in the liver. Note that ammonia and carbon dioxide are produced in the reactions, they do not enter the proximal convoluted tubule, therefore the molar fractions of these substances are $x_{NH_3,3} = x_{CO_2,3} = 0$. Insulin does not participate in any chemical reaction because its function is related to the inhibition of glucose production, thus $\sigma_{Ins,i} = 0$. Also, the sum of the four terms $r_{EGP,i}$ is considered as the total renal endogenous glucose production. With the above in mind, the following general equation represents the dynamic behavior of each substance j in the proximal convoluted tubule

$$\frac{dN_{j,II}}{dt} = x_{j,3}\,\dot{n}_3 - x_{j,4}\,\dot{n}_4 + \sum(r_{EGP,i}\,\sigma_{j,i}) - r_j \tag{11}$$

where $N_{j,II}$ are the total moles of component j in the PS_{II}, $x_{j,3}$ is the molar fraction of component j entering the proximal convoluted tubule to react mainly with water, $x_{j,4}$ is the molar fraction of component j that continues to flow into the proximal tubule to reach the loop of Henle. It is assumed that all the precursors are fully filtered from the bloodstream. However, how much the reactions progress exactly is unknown, and probably not all the available reactant is consumed. r_j represents the consumption or clearance of the substance j by the renal cells. The term $r_j = 0$ for the precursors, as well as for water, carbon dioxide, and ammonia, but $r_j \neq 0$ for glucose and insulin. In the balance equation for glucose, $r_j = r_{cgc}$ and is the rate of cells glucose consumption for their metabolic processes. In the balance equation for insulin, $r_j = r_{ic}$ and is the insulin clearance in the kidneys. Using the perfect mixing condition of all substances into the proximal convoluted tubule: $x_{j,II} = x_{j,4}$, the total mass in kmol of substance j could be expressed as $N_{j,II} = x_{j,4}N_{II}$. Applying the chain rule with the equivalence $N_{j,II} = x_{j,4}\,N_{II}$ and replacing this expression in 11 gives

$$x_{j,4}\frac{dN_{II}}{dt} + N_{II}\frac{dx_{j,4}}{dt} = x_{j,3}\,\dot{n}_3 - x_{j,4}\,\dot{n}_4 + \sum(r_{EGP,i}\,\sigma_{j,i}) - r_j \tag{12}$$

Substituting Equation 6 in Equation 12 and solving for $\frac{dx_{j,4}}{dt}$ provides:

$$\frac{dx_{j,4}}{dt} = \frac{1}{N_{II}}\left(x_{j,3}\,\dot{n}_3 - x_{j,4}\,\dot{n}_4 + \sum(r_{EGP,i}\,\sigma_{j,i}) - r_j - x_{j,4}\,\dot{N}_{II}\right) \tag{13}$$

where parameter $\dot{N}_{II} = \frac{dN_{II}}{dt}$.

3.2.4. PS_{III} - Proximal tubule where reabsorption occurs

The proximal tubule where reabsorption happens is considered a continuous filter that separates the substances that the body must conserve and the substances that must be eliminated.

Total mass balance. The total mass balance of this PS is

$$\frac{dM_{III}}{dt} = \dot{m}_4 - \dot{m}_5 - \dot{m}_6 \tag{14}$$

where M_{III} is the total mass of substances in the proximal tubule where reabsorption takes place, $\dot{m}_4$ is the mass flow coming from the proximal convoluted tubule, equivalent to $\dot{n}_4$ in molar units. Reabsorbed substances to the bloodstream are represented by mass flow $\dot{m}_5$, while the term $\dot{m}_6$ is the mass flow of the substances flowing into the loop of Henle to be eliminated in the urine; that is, substances that were not reabsorbed into the bloodstream.

In this part of the long tubular portion in the nephron, the mass is not accumulated, therefore $\frac{dM_{III}}{dt} = 0$. The term $\dot{m}_4$ is calculated from the volumetric flow entering and leaving the entire proximal tubule so that the reactor operates at a constant volumetric holdup. With that in mind and solving for the mass flow of reabsorbed substances, $\dot{m}_5$, the total mass balance for PS_{III} is

$$\dot{m}_5 = \dot{m}_4 - \dot{m}_6 \tag{15}$$

Component mass balance. In this PS, the substances to be balanced are the same as in the previous PS, i.e., all reactants and products of the chemical reactions which took place in the proximal convoluted tubule. Balance for component j can be expressed in a generic form as

$$\frac{dM_{j,III}}{dt} = w_{j,4}\,\dot{m}_4 - w_{j,5}\,\dot{m}_5 - w_{j,6}\,\dot{m}_6 \tag{16}$$

where $M_{j,III}$ is the total mass of component j into the proximal tubule where the reabsorption of different substances, including glucose and proteins as the main substances reabsorbed in the glomerulus, occurs. This part of the proximal tubule is hypothesized as a filter, in which substances are separated. Thus, two internal compartments are assumed but not declared as new PSs. One for transferred mass and the other for the perfect mixing substance. In this case, there are two exit streams, one of them ($\dot{m}_5$) is the separate flow or mass transfer flow containing the reabsorbed substances separated from the fluid in the convoluted tubules to return to the bloodstream. This exit stream does not have the same concentration as the internal part of the PS and perfect agitation cannot be assumed for this stream. Fluid flows from stream 4 and continues into stream 6, for which a perfect agitation is assumed, thus the equivalence $w_{j,III} = w_{j,6}$ and $M_{j,III} = w_{j,6}\,M_{III}$ could be applied to solve the derivative of $M_{j,III}$, recalling that M_{III} is constant $\left(\frac{dM_{j,III}}{dt} = M_{III}\frac{dw_{j,6}}{dt}\right)$. Considering no mass accumulation in PS_{III}, $\frac{dw_{j,6}}{dt} = 0$. Knowing that insulin, and precursors are completely reabsorbed into the bloodstream ($w_{j,6} = 0$), the final component mass balance for component j is written as

$$w_{j,5} = \frac{w_{j,4}\,\dot{m}_4}{\dot{m}_5} \tag{17}$$

for j = Ins, Gluta, Lac, Ala, Gly. The glucose balance is expressed by

$$w_{G,5} = \frac{w_{G,4}\,\dot{m}_4 - w_{G,6}\,\dot{m}_6}{\dot{m}_5} \tag{18}$$

taking into account that $w_{G,6} = 0$ for healthy people because of the SGLT saturation, and $w_{G,6} \neq 0$ for people with hyperglycemia. This is because when the glucose in the bloodstream is

higher than 180 mg/dl, glucose is eliminated via the urine. In contrast, if a person under normal conditions is considered, the mass balance for glucose (Equation 18) is identical to Equation 17.

When considering water, its reabsorption is tightly coupled to passive sodium reabsorption, meaning that when sodium moves, water follows. Therefore, most of the solute reabsorbed in the proximal tubule is in the form of sodium bicarbonate and sodium chloride, and about 70% of the sodium reabsorption occurs here, implying that 70% of water is also reabsorbed maintaining extracellular body fluid volume. The remaining 30% continues to flow in the renal tubules to form urine, represented here as stream 6. Even though the water is filtered simultaneously in the glomeruli and the tubules for simplicity, in the model, it is assumed that all water enters the lumen of the tubules via the glomeruli (stream 8). Additionally, net water circulating in the nephron is the only water considered in the model, i.e., water flowing to keep the equilibrium with the interstitium is not taken into account. The consequence is that water is not reabsorbed into the bloodstream and thus, $w_{W,5} = 0$. Ammonia and carbon dioxide are also not reabsorbed into the bloodstream but they continue to flow in the long tubule to be eliminated via the urine, therefore $w_{NH_3,5} = w_{CO_2,5} = 0$. Hence, the generic form of the balance for W, NH_3, and CO_2 is

$$w_{j,6} = \frac{w_{j,4}\,\dot{m}_4}{\dot{m}_6} \tag{19}$$

3.2.5. PS_{IV} - Blood circulating in the kidneys

Blood circulating in the peritubular capillaries in the kidneys is hypothesized as a continuous stirred tank that homogenizes filtered and reabsorbed blood to leave the renal vein and reintegrate into the bloodstream. Balances will be calculated in units of mass to know how the concentration of glucose changes after passing through the kidneys.

Total mass balance. The total mass balance for PS_{IV} in mass units is given by

$$\frac{dM_{IV}}{dt} = \dot{m}_2 + \dot{m}_5 - \dot{m}_7 \tag{20}$$

with M_{IV} the total mass of blood contained in the system irrigating the nephrons. Since no mass accumulation is assumed, $\frac{dM_{IV}}{dt} = 0$ and the total mass balance yield

$$\dot{m}_7 = \dot{m}_2 + \dot{m}_5 \tag{21}$$

Component mass balance. Ammonia, and carbon dioxide are not reabsorbed into the blood because of the presence of water. Thus, the substances to be balanced in this PS are G, Ins, Gluta, Lac, Ala, and Gly. Balance for the substances of interest can be written in a generic form as

$$\frac{dM_{j,IV}}{dt} = w_{j,2}\,\dot{m}_2 + w_{j,5}\,\dot{m}_5 - w_{j,7}\,\dot{m}_7 \tag{22}$$

where $M_{j,IV}$ is the total mass of component j = G, Ins, Gluta, Lac, Ala, Gly, into the blood flowing through the kidneys. Using the assumption of perfect agitation, the equivalence $w_{j,IV} =$

Table 1: Equations of the model's basic structure.

Process system	Equations
PS_I	$\dot{m}_2 = \dot{m}_1 - \dot{m}_3 + \dot{m}_8$
	$w_{j,3} = \frac{w_{j,1}\,\dot{m}_1}{\dot{m}_3}$
	$w_{W,3} = \frac{w_{W,8}\,\dot{m}_8}{\dot{m}_3}$
PS_{II}	$\frac{dN_{II}}{dt} = \dot{n}_3 - \dot{n}_4 + \sum(r_{EGP,i}\,\sigma_{j,i})$
	$\frac{dx_{j,4}}{dt} = \frac{1}{N_{II}}\left(x_{j,3}\,\dot{n}_3 - x_{j,4}\,\dot{n}_4 + \sum(r_{EGP,i}\,\sigma_{j,i}) - r_j - x_{j,4}\,\dot{N}_{II}\right)$
PS_{III}	$\dot{m}_5 = \dot{m}_4 - \dot{m}_6$
	$w_{j,5} = \frac{w_{j,4}\,\dot{m}_4}{\dot{m}_5}$
	$w_{G,5} = \frac{w_{G,4}\,\dot{m}_4 - w_{G,6}\,\dot{m}_6}{\dot{m}_5}$
	$w_{j,6} = \frac{w_{j,4}\,\dot{m}_4}{\dot{m}_6}$
PS_{IV}	$\dot{m}_7 = \dot{m}_2 + \dot{m}_5$
	$\frac{dw_{j,7}}{dt} = (w_{j,5}\,\dot{m}_5 - w_{j,7}\,\dot{m}_7)\frac{1}{M_{IV}}$

$w_{j,7}$ and $M_{j,IV} = w_{j,7}M_{IV}$ can be applied to solve the derivative of $M_{j,IV}$, with M_{IV} constant. Replacing this derivative solution in Equation 22, and keeping in mind that the substances of interest are completely filtered in the glomerulus, i.e., stream 2 is free ($w_{j,2} = 0$) of those substances, the final component mass balance for component j is written as

$$\frac{dw_{j,7}}{dt} = (w_{j,5}\,\dot{m}_5 - w_{j,7}\,\dot{m}_7)\frac{1}{M_{IV}} \tag{23}$$

3.2.6. The basic structure of the model

In this section, the equations deduced from the previous steps with relevant information to answer the model question are taken to form the model's basic structure. Consequently, the equations with valuable information for PS_I are 2, 4, and 5, keeping in mind that Equation 4 produces six other equations, one for every component j: glucose (G), insulin (Ins), glutamine (Gluta), lactate (Lac), alanine (Ala), and glycerol (Gly). For PS_{II} the equations are 6 and 13, considering in the case of Equation 13, j as glucose (G), insulin (Ins), glutamine (Gluta), lactate (Lac), alanine (Ala), glycerol (Gly), water (W), ammonia (NH_3), and carbon dioxide (CO_2), producing nine other equations. For PS_{III} the equations are 15, 17, 18, 19, keeping in mind that Equation 18 is valid for people with diabetes, but for people under usual conditions, Equation 17 is also valid for glucose. Additionally, Equation 17 produces five other equations, one for every component j: Ins, Gluta, Lac, Ala, and Gly. Equation 19 produces three other equations: water, NH_3, and CO_2. Finally, for PS_{IV}, the equations with relevant information are 21 and 23, where Equation 23 produces six other equations, one for every component j: G, Ins, Gluta, Lac, Ala, and Gly. Consequently, the model's basic structure has 35 equations which are summarized in Table 1.

Table 2: Model variables, structural parameters, and structural constants.

	PS_I	PS_{II}	PS_{III}	PS_{IV}	Total
Variables	$\dot{m}_2, w_{j,3}, w_{W,3}$	$N_{II}, x_{j,4}$	$\dot{m}_5, w_{j,5}, w_{G,5}, w_{j,6}$	$\dot{m}_7, w_{j,7}$	35
Structural Parameters	$\dot{m}_1, \dot{m}_3, \dot{m}_8$ $w_{j,1}, w_{W,8}$	$\dot{n}_3, \dot{n}_4, r_{EGP,i}$ $r_j, \dot{N}_{II}$	$\dot{m}_4, \dot{m}_6, w_{G,6}$	M_{IV}	23
Structural Constants	-	$\sigma_{j,i}$	-	-	15

The indexes are j = G, Ins, Gluta, Lac, Ala, Gly, W, NH_3, CO_2; i (via of biochemical reactions): 1 =Gluta, 2 =Lac, 3 =Ala, 4 =Gly.

3.2.7. Variables, structural parameters, and structural constants

In this step, the symbols forming the equations selected for the basic structure of the model previously reported are classified as variables, structural parameters, and constants. Variables are defined here as the unknowns that will be solved by the model, and they are intentionally set on the left side of the equations, while constants are universal values or fixed values determined by the modeler. Note that the structural parameters have not been calculated yet or nor have they been replaced in the equations by their numerical values. This is intended to avoid those structural parameters from losing their inherent interpretability as a result of their origin, directly from the application of the conservation law in each PS. To calculate them, new levels of specification will be opened, where the functional parameters will be defined [32], as established in the following step. A summary with the model variables and both structural parameters and constants for every PS is provided in Table 2.

Note that $w_{j,3}$ is declared as a variable of PS_I, therefore, $x_{j,3}$ is also considered as a variable and not as a structural parameter. This equivalence is directly deduced through units conversion. Additionally, $w_{j,4}$ is the variable $x_{j,4}$ but in mass units, hence, $w_{G,4}$ and $w_{W,4}$ too have to be solved by the model.

3.2.8. Constitutive and assessment equations for structural and functional parameters and definition of constants

Constitutive and assessment equations are generally algebraic equations used to define unknown parameters of every process system. A constitutive equation approximates the response of a physical quantity to external stimuli using a law or principle. Darcy's law, Arrhenius' law, heat, mass, and the momentum rate of transfer laws, among others, are examples of constitutive equations. In some cases, when it is not possible to use a law or principle to define an unknown parameter, an empirical correlation could be used. On the other hand, an assessment equation is a mathematical relation to assess a parameter's numerical value, without any intention of descriptively linking the calculated numerical value to the phenomena occurring in the process being modeled. New

parameters appearing in the constitutive equations are called functional parameters. Constitutive and assessment equations used to define both structural and functional parameters make up the extended structure of the model [32].

When a new mathematical equation is used to define a parameter, a new specification level appears. The specification level can offer new insights into the process and can provide useful information to produce the output of the model. In other words, the specification levels can increase knowledge regarding the process of interest. New specification levels will be opened until having all parameters of the model defined as a numerical value. Constitutive and assessment equations of the extended structure are determined by the modeler because each equation can be stated with a different level of detail following the specific modeler preferences or available knowledge of the phenomena [32].

Constitutive and assessment equations which define the structural parameters of the model of the kidneys and their role in glucose metabolism are reported in Table 3. Table 4 reports constitutive equations that define the model's functional parameters. In these tables, the columns report the number of equations generated when the parameter is defined. Finally, assessment equations or values of fixed functional parameters and constants of the model are given in Table 5. The procedure to establish numerical values to identified parameters follows the typical gradient method so as to reduce the model prediction error for real data available in the literature. However, the numerical values are only optimal for the process of interest in the modeled phenomena, but nothing can be said about their uniqueness or the robustness of the steady-state values found, as a sensitivity analysis was not conducted. Note that, as previously mentioned, symbols $w_{j,4}$ and $x_{j,3}$ are considered the same variables as $x_{j,4}$ and $w_{j,3}$, respectively. However, these species are different, variables $x_{j,k}$ are expressed in molar fraction units, whereas $w_{j,k}$ are assumed in mass fraction. The conversion between the two variables occurs through the molecular mass of substance j, a trivial equation not included in the model. The constant molecular mass of the water $\mathfrak{M}_W$ is included in the evaluation of the functional parameter $\mathfrak{M}_j$.

3.2.9. Degrees of freedom analysis

The mathematical model can be solved only if the number of unknowns in the model, which includes variables and both structural and functional parameters of the model, and the number of equations is equal; that is, if the model's degrees of freedom are equal to zero. The analysis of the degrees of freedom of the derived model is summarized in Table 6. Constitutive equations to define functional parameters reported in Table 4 and assessment equations to define functional parameters reported in Table 5 are considered in the total number of functional parameters reported in Table 6.

Table 3: Constitutive and assessment equations for structural parameters of the model.

#	Description	Constit. and Asses. Equation	Instances	Reference
1	Mass flow rate of blood entering the kidneys (stream 1).	$\dot{m}_1 = \rho_b \dot{V}_b$	1	[36]
2	Mass flow rate of components of interest filtered in the glomerulus (stream 3).	$\dot{m}_3 = \dot{m}_1 \sum_j w_{j,1} + \dot{m}_8 w_{W,8}$	1	[36]
3	Mass flow rate of components entering the glomerulus from the interstitium (stream 8).	$\dot{m}_8 = w_{W,6} \dot{m}_6 + \dot{n}_{W,rx} \mathfrak{M}_W$	1	[36]
4	Mass fraction of component j entering the kidneys by the renal artery.	$w_{j,1} = C_{j,1} \frac{1}{\rho_b} \mathfrak{M}_j$	6	UC
5	Mass fraction of water entering the glomerulus from the interstitium.	$w_{W,8} = 1$	1	A
6	Molar flow of mix being filtered in the glomerulus.	$\dot{n}_3 = \sum_j \dot{n}_{j,3}$	1	[36]
7	Molar flow of reaction products in the proximal tubule.	$\dot{n}_4 = \frac{\dot{V}_4 \rho_{mix}}{\mathfrak{M}_{mix}}$	1	UC
8	Reaction velocity of endogenous glucose production via non-glucidic precursors, with $j : Gluta, Lac, Ala, Gly$.	$r_{EGP_i} = k_{0,EGP_i} C_{j,4} e^{\frac{-Ea_{EGP_i}}{RT}}$	4	[36]
9	Rate of cell glucose utilization in the kidneys.	$r_{cgc} = 11.1 - 55 \frac{\mu mol}{(Kg - min)}$	1	[30]
10	Reaction of insulin degradation in the kidneys.	$r_{ic} = k_{0,Ins} C_{Ins,4} e^{(\frac{-Ea_{Ins}}{RT})}$	1	[30]
11	Differential of total mass in molar units of substances in PS_{II}	$\dot{N}_{II} = \sum \dot{N}_{j,II}$	1	A
12	Mass flow of reaction products in the proximal tubule.	$\dot{m}_4 = \dot{n}_4 \mathfrak{M}_{mix}$	1	UC
13	Mass flow of reaction products going to the collecting duct.	$\dot{m}_6 = \dot{V}_u \rho_u$	1	[36]
14	Mass fraction of glucose in the urine.	$w_{G,6} = \frac{\dot{m}_{G,6}}{\dot{m}_6}$	1	[36]
15	Total mass of blood flowing the kidneys.	$M_{IV} = \rho_b V_b$	1	[36]

Abbreviations. UC: unit conversion, A: assumed. Indexes j = G, Ins, Gluta, Lac, Ala, Gly, W, NH_3, CO_2. Indexes i (via biochemical reactions): 1 =Gluta, 2 =Lac, 3 =Ala, 4 =Gly.

Table 4: Constitutive equations for functional parameters of the model.

#	Description	Constit. and Asses. Equation	Instances	Reference
1	Molar flow of substances of interest being filtered in the glomerulus.	$\dot{n}_{j,3} = \dot{n}_{j,1} + \dot{n}_{W,8}$	7	[36]
2	Molar flow of substances of interest entering the kidneys by the renal artery.	$\dot{n}_{j,1} = \frac{\dot{m}_1 w_{j,1}}{\mathfrak{M}_j}$	6	UC
3	Volumetric flow of products of reactions taking place in proximal tubule.	$\dot{V}_4 = \sum \dot{V}_{j,3}$	1	A
4	Density of mix (all components) in the reactor representing the first part of proximal tubule.	$\rho_{mix} = \frac{1}{\sum \frac{w_{j,4}}{\rho_j}}$	1	[36]
5	Molar mass of mix (all components) in the reactor representing the first part of proximal tubule.	$\mathfrak{M}_{mix} = \sum x_{j,4}\, \mathfrak{M}_j$	1	[37]
6	Volumetric flow of substances entering the proximal tubule.	$\dot{V}_3 = \sum \dot{V}_{j,3}$	1	A
7	Volumetric flow of component j filtered in the glomerulus.	$\dot{V}_{j,3} = \dot{n}_{j,3}\, \mathfrak{M}_j\, \frac{1}{\rho_j}$	7	[36]
8	Molar-volumetric concentration of component j, after every gluconeogenesis reaction i (in stream 4).	$C_{j,4} = \frac{x_{j,4}\, \rho_{mix}}{\mathfrak{M}_{mix}}$	9	[36]
9	Mass flow of glucose in the urine. It is zero in healthy people.	$\dot{m}_{G,6} = \begin{cases} 0 \rightarrow w_{G,1} < w_{G,Lim} \\ \dot{m}_1 (w_{G,1} - w_{G,Lim}) \rightarrow w_{G,1} > w_{G,Lim} \end{cases}$	1	O
10	Mass fraction limit of glucose absorbed by the kidneys.	$w_{G,Lim} = C_{G,Lim} \frac{\mathfrak{M}_G}{\rho_b}$	1	UC

Abbreviations. O: own equations, UC: unit conversion, A: assumed. Indexes j = G, Ins, Gluta, Lac, Ala, Gly, W, NH_3, CO_2. Indexes i (via biochemical reactions): 1 =Gluta, 2 =Lac, 3 =Ala, 4 =Gly.

Table 5: Assessment equations for functional parameters of the model. The numerical values are fixed parameters in the model. Constants of the model are also reported in this table shown in the "value" column.

Symbol	Description	Value	Reference
ρ_b	Density of the blood.	1060 kg/m^3	[20]
$\dot{V}_b$	Volumetric flow of blood irrigating the kidneys.	1.2 L/min	[20]
$\dot{n}_{W,rx}$	Number of moles of water consumed during the reactions in the proximal tubule per second.	9.1749 $\mu mol/s$	[20]
$C_{j,1}$	Molar-volumetric concentration of component j at blood entering the kidneys.		[36]
$\mathfrak{M}_j$	Molar mass of component j (known value).		A
ρ_j	Density of component j (known value).		A
k_{0,EGP_1}	Glucose production rate constant via glutamine in the proximal tubule.	107.9 $\times 10^{-9}\, m^3/s$	I
k_{0,EGP_2}	Glucose production rate constant via lactate in the proximal tubule.	35.2 $\times 10^{-13}\, m^3/s$	I
k_{0,EGP_3}	Glucose production rate constant via alanine in the proximal tubule.	52.5 $\times 10^{-10}\, m^3/s$	I
k_{0,EGP_4}	Glucose production rate constant via glycerol in the proximal tubule.	60.5 $\times 10^{-11}\, m^3/s$	I
$k_{0,Ins}$	Insulin clearance rate constant in the proximal tubule.	0.85 $\times 10^{-6}\, m^3/s$	I
Ea_{EGP_1}	Activation energy of glucose production via glutamine.	3.55 $\times 10^7\, kJ/kmol$	I
Ea_{EGP_2}	Activation energy of glucose production via lactate.	8.9 $\times 10^6\, kJ/kmol$	I
Ea_{EGP_3}	Activation energy of glucose production via alanine.	2.82 $\times 10^7\, kJ/kmol$	I
Ea_{EGP_4}	Activation energy of glucose production via glycerol.	2.18 $\times 10^7\, kJ/kmol$	I
Ea_{Ins}	Activation energy of insulin clearance in the kidneys.	35000 $kJ/kmol$	I
R	Universal constant for ideal gas.	8.314 $J/molK$	[36]
T	Corporal temperature.	37 $^\circ C$	[38]

Abbreviations. I: identified, A: assumed. Indexes j = G, Ins, Gluta, Lac, Ala, Gly, W, NH_3, CO_2. Indexes i (via biochemical reactions): 1 =Gluta, 2 =Lac, 3 =Ala, 4 =Gly.

Symbol	Description	Value	Reference
$\dot{V}_u$	Volumetric flow leaving from collecting duct to form urine.	$1.5L/dia$	[20]
ρ_u	Density of urine.	$1017.5g/L$	[20]
$C_{G,Lim}$	Concentration limit of glucose absorbed by the kidneys.	$180mg/dl$	[20]
V_b	Blood volume irrigating the kidneys.	$0.60, mL$	[20]
$\sigma_{j,i}$	Stoichiometric coefficient for j= glutamine, lactate, alanine, glycerol, and water in the reaction i.	-1	[33, 34, 35]
$\sigma_{j,1}$	Stoichiometric coefficient for j= ammonia, carbon dioxide in the reaction of glucose production via glutamine.	2	[33, 34, 35]
$\sigma_{G,i}$	Stoichiometric coefficient for glucose production in the reaction i.	0.5	[33, 34, 35]
$\sigma_{W,1}$	Stoichiometric coefficient for water in the reaction of glucose production via glutamine.	-5	[33, 34, 35]
$\sigma_{W,2}$	Stoichiometric coefficient for water in the reaction of glucose production via lactate.	-3	[33, 34, 35]
$\sigma_{W,3}$	Stoichiometric coefficient for water in the reaction of glucose production via alanine.	-4	[33, 34, 35]
$\sigma_{NH_3,3}$	Stoichiometric coefficient for ammonia in the reaction of glucose production via alanine.	1	[33, 34, 35]

Abbreviations. I: identified, A: assumed. Indexes: j = G, Ins, Gluta, Lac, Ala, Gly, W, NH_3, CO_2. Indexes i (via biochemical reactions): 1 =Gluta, 2 =Lac, 3 =Ala, 4 =Gly.

Table 6: Degrees of Freedom.

	V	**SP**	**FP**	**Net**	**DoF**
Equations	35	23	58	116	0
Unknowns	35	23	58	116	

Abbreviations. V: variables, SP: structural parameters, FP: functional parameters, Net: sum of $SP + FP + V$, and DoF: degrees of freedom (difference between unknowns and equations).

3.3. Simulation of the computational model

3.3.1. Computational model construction

The model was programmed and solved using MatLab®.

3.3.2. Model Validation

The mathematical model was fitted to data reported in the literature but a real validation with data taken in real patients is still pending. The strategy to fit the mathematical model is discussed extensively in the next section.

4. Results and discussion

This section presents the results of a $1.5\,h$ simulation of the renal model and its role in glucose metabolism for a person under normal conditions. As mentioned earlier, a validation model using real data has not yet been tested. However, following a broad range of published data (see Table 7), the results of the model were compared according to the available physiological knowledge in the literature. The final steady-state values of the variables were adjusted following the data in the literature. The model is also intended to describe the dynamic behavior of glucose as it passes through the kidneys. However, an experimental evaluation of the dynamic behavior is not possible as, to date, the required data have not been available. Most of the data report the rate of glucose release into the circulation by kidneys for the post-absorptive state, including specific data for every main non-carbohydrate precursor. Around 20-25% of glucose released into the circulation after overnight fasting comes from the kidneys, and the remaining 75-80% comes from the liver. In contrast and surprisingly, in the postprandial state, renal gluconeogenesis increases approximately twofold and around 60% of glucose is released into the circulation, as indicated in Table 7. In contrast to the percentage of glucose production in the kidneys, which is known, the amount of glucose derived from every non-carbohydrate precursor in the postprandial state is not known. Table 7 shows the average values for each precursor based on all data found in the literature. Values for the utilization of each precursor are calculated based on the stoichiometric equations previously reported in Section 3.2.

Table 7 shows that the glucose production derived from glutamine is around $0.623\,\mu mol/s$ when using $1.246\,\mu mol/s$ of glutamine. This value corresponds to 4% of total glucose released into the circulation. In turn, lactate is more freely available in the blood, therefore, glucose production from lactate is estimated as $\sim 1.557\,\mu mol/s$, representing a 10% of the total glucose production in the kidneys. Alanine and glycerol precursors produce $0.467\,\mu mol/s$ and $0.311\,\mu mol/s$, respectively, corresponding to 3% and 2% of the total renal gluconeogenesis. The results of the model are illustrated by the following. Figure 4 illustrates the total renal glucose production in both postprandial and post-absorptive states, once again evincing that the model responses reach the numerical values reported in Table 7. Solid lines indicate the model response and dashed

Table 7: Data for renal endogenous glucose production (EGP) in both post-absorptive and postprandial state.

	Precursor	Renal EGP $[\mu mol/s]$	Precursor utilization $[\mu mol/s]$	% Overall rate of glucose production	Reference
Post-absorptive state	Glutamine	0.623 (4%)	1.246	20-25%	[28, 33, 39]
	Lactate	1.557 (10%)	3.114		
	Alanine	0.467 (3%)	0.934		
	Glycerol	0.311 (2%)	0.622		[22, 30, 40]
	Other	0.156 (1%)	-		
Post-prandial state		8.647		60%	[41, 39, 42]

lines are the reference values taken from the literature. During the postprandial state, the model response shows a renal glucose production of $8.569\,\mu mol/s$, corresponding to 60% of the total glucose released into the bloodstream. This value is close to the reference value of $8.647\,\mu mol/s$ represented with dashed lines. For the post-absorptive state, the model response indicates a renal glucose production of $2.955\,\mu mol/s$, which is almost the same reference value as the dashed lines, i.e., $3.11\,\mu mol/s$, representing almost 20% of the total glucose released into the bloodstream. It is worth clarifying that the computational model was solved only for the post-absorptive state because the rate of glucose production for each precursor is available in the literature for this state. However, for the postprandial state, the total percentage of glucose produced is known but the amount produced by each precursor is not specified. In this sense and knowing that in the postprandial state the kidneys produce around 60% of the total glucose in the post-absorptive state, the results for this state were multiplied by 2.9 to obtain the postprandial state, in accordance with [30].

Renal gluconeogenesis for the different precursors is shown in Figure 5, where the amount of glucose production from every non-carbohydrate precursor (shown in solid black lines) reaches the average values previously reported (dashed gray line), proving correct behavior of the model predictions. In this sense, the model responses show a renal glucose production via glutamine of $0.6162\,\mu mil/s$, via lactate of $1.553\,\mu mol/s$, via alanine of $0.4766\,\mu mol/s$, and via glycerol of $0.308\,\mu mol/s$. These values are very close to the reference values derived from the literature [27, 30, 41, 33, 29, 24, 42] and reported in Table 7.

The available literature on glucose metabolism in the kidneys reports more studies focusing on an analysis of the metabolism of precursors in the kidneys than on glucose production itself. It is worth remembering that the result illustrated in Figure 5 illustrates the glucose production in the kidneys during the post-absorptive state and that a similar curve is not possible for the post-

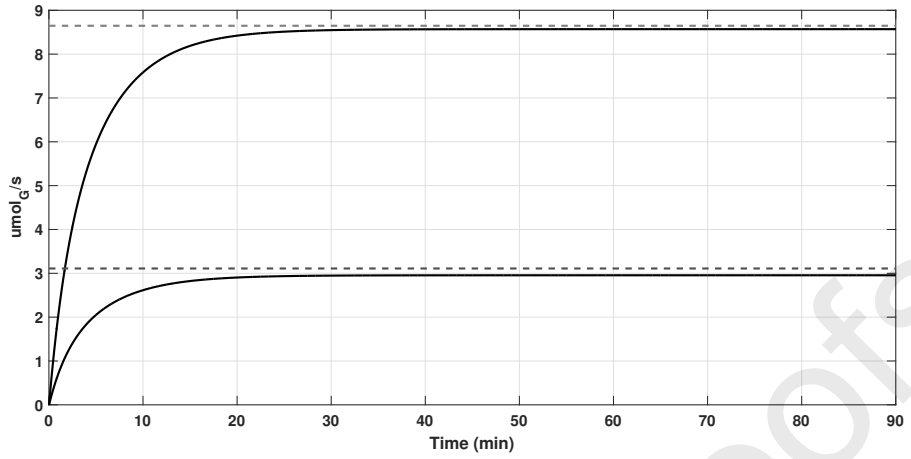

Figure 4: Renal gluconeogenesis in postprandial (upper curve) and post-absorptive state (lower curve). Solid curves are the model response and dashed lines are values of the experimental data reported in the literature. In the postprandial state, the solid line reaches a renal glucose production of $8.569\,\mu mol/s$, whereas for the post-absorptive state, the solid line reaches a renal glucose production of $2.955\,\mu mol/s$. The output quantities reported in the figure are computed from the state variables of the Equation 13, but expressed in $\mu mol/s$ units.

prandial state because the literature does not report the amount of glucose production via every non-carbohydrate precursor, but rather the total glucose production. Additionally, it is important to mention that the role of hormones such as insulin and glucagon was not considered in the model. The role of the glucagon in renal glucose production is not evinced in the literature, and insulin is assumed to be produced and released in the pancreas according to glucose concentration. Insulin decreases glycerol uptake and increases lactate uptake in the kidneys, reducing renal glucose production probably not only due to the reduction of the substrates but also because of other intrarenal mechanisms [28]. On the other hand, the concentration of epinephrine, rather than that of glucagon, is responsible for the increased renal glucose production.

Recalling that the kidneys act as controlling agents by keeping an equilibrium between the blood glucose concentration in the renal artery and renal vein, evidence of this by the model responses is given in Figure 6. This means that when a person under normal conditions who has a blood glucose concentration around of $90mg/dl$ in the renal artery, the glucose concentration in the renal vein will also be around $90mg/dl$. This fact also implies a proportional response in the renal vein to the renal artery when blood glucose concentration increases after a meal (postprandial state). It is also important to mention that the kidneys are not responsible for the complete control of the glucose concentration in the human body. This homeostasis mechanism is conducted jointly by several organs. For this reason, in Figure 6, the dynamic response does not reach the desired steady-state. However, the glucose concentration in the renal vein is close to glucose concentration in the renal artery. The difference is approximately $1mg/dL$. Here, the simulation time taken to obtain the steady-state of glucose concentration in the renal vein is of 4.0 hours.

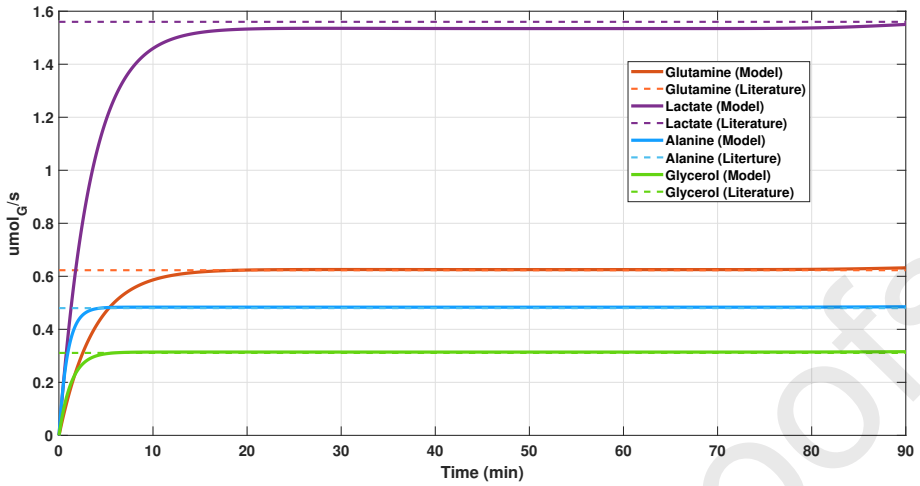

Figure 5: Renal endogenous glucose production via main non-carbohydrate precursors during post-absorptive state. Dashed lines indicate reference values taken from the literature and solid lines are the model responses of glucose production via every precursor. Lactate produces about 10% glucose, 4% glutamine, 3% alanine, and 2% glycerol, for a total glucose production of approximately 20-25% of the total glucose released into the bloodstream.

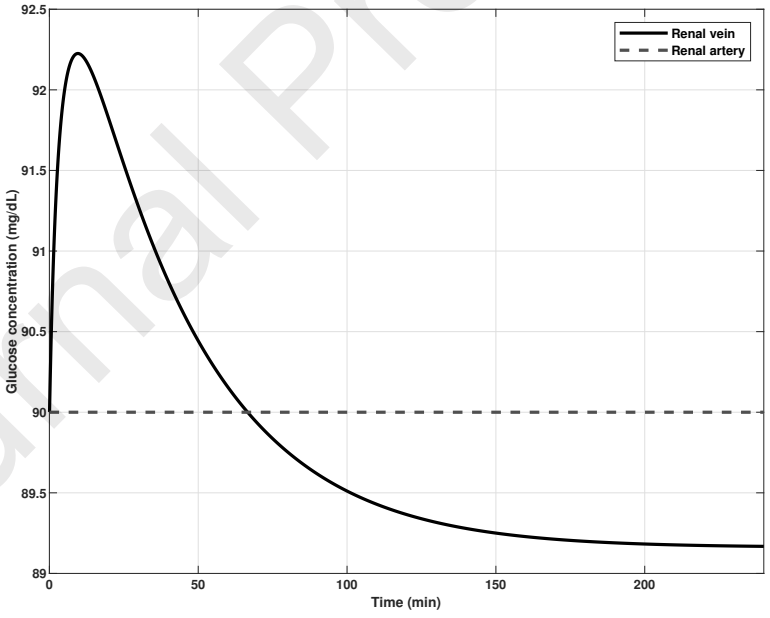

Figure 6: Dynamics of the glucose concentration entering the kidneys via renal artery and leaving the kidneys via renal vein. An equilibrium between both blood vessels is evident, indicating the kidneys' ability to regulate blood glucose concentrations.

Figure 7 shows the concentration of every precursor after passing the nephrons. Observe that the concentration decreases because the precursors have reacted to produce glucose and the remaining

quantity is reabsorbed into the bloodstream. The dynamic behavior for each precursor assumes an initial value for each substance as if the kidneys start to consume them at time zero. The time is given in minutes to illustrate the dynamic response. Additionally, the precursors that enter the kidneys were assumed to be used to producing glucose and the amount that is reabsorbed into the bloodstream is almost nil [22, 30, 28, 40, 33, 39].

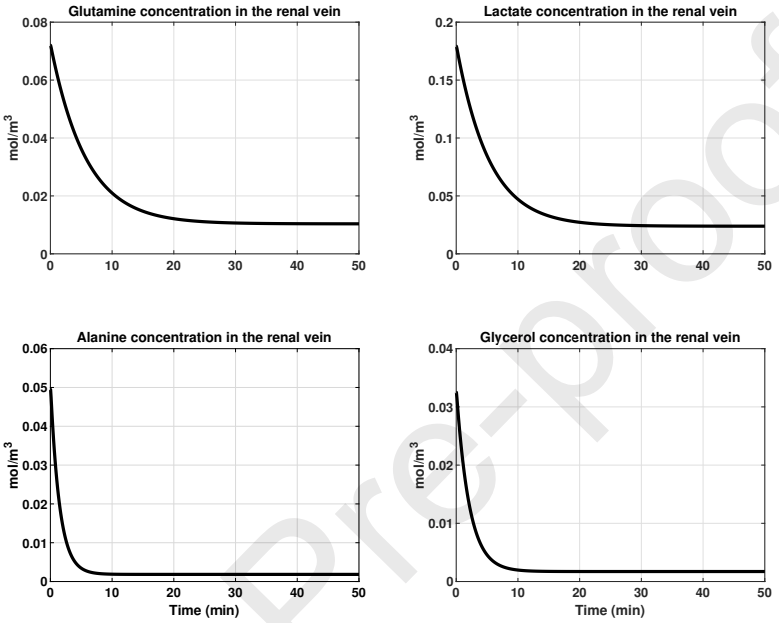

Figure 7: Concentration of every precursor leaving the kidneys via renal vein. Due to the assumption that the kidneys capture only the amount of substrate required to produce glucose, the amount of precursor that is reabsorbed into the blood is almost zero.

Finally, the model can regulate the glucose levels in the bloodstream of a person under normal conditions, in which case, the renal excretion of the glucose via urine is void when the glucose levels are lower than $180\,mg/dL$, as shown in Figure 8. Here, the dashed line represents the glucose concentration in blood (mg/dL) (i.e., value in left y-axis), while the continuous line is the glucose concentration in urine (right y-axis). Although a normal blood glucose concentration is considered in the model and its simulation, the model is subjected to a hyperglycemic condition after 80 minutes in order to assess the model response under changes in the blood glucose levels. A hyperglycemic condition causes a small amount of glucose to be excreted in the urine. This phenomenon is called glycosuria based on serum glucose concentration. This coincides with the behavior of the kidneys in a person with high blood glucose levels, like in people suffering from diabetes mellitus.

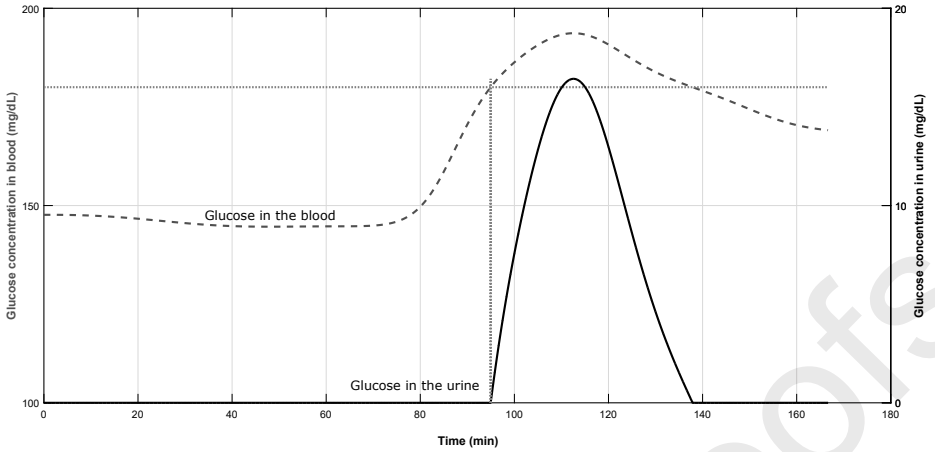

Figure 8: Renal glucose excretion via urine (right y-axis) when the blood glucose concentration (left y-axis) is upper than $180\,mg/dL$. This behavior, known as glycosuria, is often observed in people with diabetes mellitus.

5. Conclusion

The kidneys' contributions to maintaining glucose homeostasis include an important production of glucose via gluconeogenesis. Besides its filtration, reabsorption, renal glycolysis, and, under particular conditions such as hyperglycemia, glucose can be excreted via the urine to eliminate the excess in the blood. In the present work, a phenomenological-based semi-physical model of the role of the kidneys in glucose metabolism is presented. Most of the parameters of the model are interpretable, i.e., the model includes parameters with a coherent physiological meaning in the modeling process of interest. To the best of the authors' knowledge, this model is the first mathematical model describing all reported physiological aspects of the kidneys involved in the glucose regulation system. The model's results reproduce the data found in literature and reflect the available physiological knowledge about the kidney's functions. Thus, this model could be used in combination with other models to form a model-base control structure to examine the possible provision of an artificial pancreas.

References

[1] R. N. Bergman, Minimal model: perspective from 2005, Hormone Research in Paediatrics 64 (2005) 8–15. doi:10.1159/000089312.

[2] A. Boutayeb, A. Chetouani, A critical review of mathematical models and data used in, BioMedical Engineering OnLine 9 (2006) 1–9. doi:10.1186/1475-925X-5-43.

[3] A. Makroglou, J. Li, Y. Kuang, Mathematical models and software tools for the glucose-insulin regulatory system and diabetes: an overview, Applied Numerical Mathematics 56 (3) (2006) 559 – 573. doi:https://doi.org/10.1016/j.apnum.2005.04.023.

[4] C. Cobelli, C. D. Man, M. G. Pedersen, A. Bertoldo, G. Toffolo, Advancing our understanding of the glucose system via modeling: A perspective, IEEE Transactions on Biomedical Engineering 61 (5) (2014) 1577–1592.

[5] S. Contreras, D. Medina-Ortiz, C. Conca, l. Olivera-Nappa, A novel synthetic model of the glucose-insulin system for patient-wise inference of physiological parameters from small-size ogtt data, Frontiers in Bioengineering and Biotechnology 8 (2020) 195. doi:10.3389/fbioe.2020.00195.

[6] R. Rabkin, A. Rubenstein, J. Colwell, Glomerular filtration and proximal tubular absorption of insulin 125 i, American Journal of Physiology-Legacy Content 223 (5) (1972) 1093–1096, pMID: 4654343. doi:10.1152/ajplegacy.1972.223.5.1093.

[7] C. F.A., P. D.R., Hydrolysis and transport of small peptides by the proximal tubule, American Journal of Physiology-Renal Physiology 238 (3) (1980) F151–F158, pMID: 6989268. arXiv:https://doi.org/10.1152/ajprenal.1980.238.3.F151, doi:10.1152/ajprenal.1980.238.3.F151.

[8] R. Rabkin, J. Jones, A. E. Kitabchi, Insulin Extraction from the Renal Peritubular Circulation in the Chicken, Endocrinology 101 (6) (1977) 1828–1833. arXiv:https://academic.oup.com/endo/article-pdf/101/6/1828/10677611/endo1828.pdf, doi:10.1210/endo-101-6-1828.

[9] C. Dalla Man, F. Micheletto, D. Lv, M. Breton, B. Kovatchev, C. Cobelli, The UVA/PADOVA Type 1 Diabetes Simulator: New Features., Journal of diabetes science and technology 8 (2014) 26–34. doi:10.1177/1932296813514502.

[10] R. Visentin, C. Dalla Man, B. Kovatchev, C. Cobelli, The university of virginia/padova type 1 diabetes simulator matches the glucose traces of a clinical trial., Diabetes technology & therapeutics 16 (7) (2014) 428–34. doi:10.1089/dia.2013.0377.

[11] D. Basmadjian, R. Farnood, The Art of Modeling in Science and Engineering with Mathematics, 2nd Edition, Chapman and Hall/CRC, 2006.

[12] T. G. Dobre, J. G. S. Marcano, Chemical Engineering: Modelling, Simulation and Similitude, Wiley-VCH Verlag GmbH & Co. KGaA, Alemania, 2007. doi:10.1002/9783527611096.

[13] K. Hangos, I. T. Cameron, Process Modelling and Model Analysis, Vol. 4, Academic Press, 2001. arXiv:9809069v1, doi:10.1007/s13398-014-0173-7.2.

[14] I. Herrera, J. F. Pinder, Mathematical modeling in sciencie and engineering, John Wiley & Sons, Ltd, New Jersey, 2012.

[15] W. L. Luyben, Process modeling, simulation, and control for chemical engineers, 2nd Edition, McGraw-Hill, 1990.

[16] T. E. Marlin, Process control: designing process and systems for dynamic performance, 2nd Edition, McGraw-Hill, Inc, USA, 1995.

[17] R. L. Woods, K. L. Lawrence, Modeling and Simulation of Dynamic Systems, 1st Edition, Pearson, USA, 1997.

[18] H. Alvarez, P. Vega, S. Revollar, R. Lamanna, Metodología para la Obtención de Modelos Semifísicos de Base Fenomenológica Aplicada a una Sulfitadora de Jugo de Caña de Azúcar, Journal: Revista Iberoamericana de Automática e Informática Industrial RIAI 6 (3) (2009) 10–20. doi:10.1016/S1697-7912(09)70260-2.

[19] L. Lema-Perez, J. Garcia-Tirado, C. Builes-Montaño, H. Alvarez, Phenomenological-Based model of human stomach and its role in glucose metabolism, Journal of Theoretical Biology 460 (2019) 88–100. doi:10.1016/j.jtbi.2018.10.024.

[20] A. C. Guyton, J. E. Hall, Textbook of medical physiology, 7th Edition, Philadelphia, Pennsylvania, 2006.

[21] A. Mather, C. Pollock, Glucose handling by the kidney, International Society of Nephrology 79 (2011) s1–s6. doi:http://dx.doi.org/10.1038/ki.2010.509.

[22] J. E. Gerich, C. Meyer, H. J. Woerle, M. Stumvoll, Renal gluconeogenesis its importance in human glucose homeostasis, Diabetes Care 24 (2001) 382–391.

[23] R. Bellomo, Bench-to-bedside review: Lactate and the kidney, Critical Care 6 (2002) 322–326.

[24] D. I. Weiner, J. W. Verlander, Renal ammonia metabolism and transport, Comprehensive Physiology 3 (2013) 201–220. doi:10.1002/cphy.c120010.

[25] M. Chamberlain, L. Stimmler, The renal handling of insulin, Journal of Clinical Investigation 46 (1967).

[26] P. Cersosimo, Eugenioand Garlick, F. John, Renal glucose production during insulin-induced hypoglycemia in humans, Diabetes 48 261–266.

[27] E. Cersosimo, P. Garlick, F. John, Renal substrate metabolism and gluconeogenesis during hypoglycemia in humans, Diabetes 49 (2000) 1186–1193.

[28] C. Meyer, J. M. Dostou, J. E. Gerich, Role of the human kidney in glucose counterregulation, Diabetes 48 (1999) 943–948.

[29] C. L. Triplitt, Understanding the kidneys' role in blood glucose regulation, Am J Manag Care 18 (1 Suppl) (2012) S11–6.

[30] J. E. Gerich, Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications, Diabetic Medicine 27 (2010) 136–142. doi:10.1111/j.1464-5491.2009.02894.x.

[31] D. Basu, R. Kulkarni, Overview of blood components and their preparation, Indian journal of anaesthesia 58 (2014) 529–537. doi:10.4103/0019-5049.144647.

[32] L. Lema-Perez, R. Muñoz-Tamayo, J. Garcia-Tirado, H. Alvarez, On parameter interpretability of phenomenological-based semiphysical models in biology, Informatics in Medicine Unlocked 15 (November 2018) (2019) 100158. doi:10.1016/j.imu.2019.02.002.

[33] M. Stumvoll, G. Perriello, C. Meyer, J. Gerich, Role of glutamine in human carbohydrate metabolism in kidney and other tissues, Kidney International 55 (3) (1999) 778–792. doi:10.1046/j.1523-1755.1999.055003778.x.

[34] J. Boyle, Lehninger principles of biochemistry (4th ed.): Nelson, D., and Cox, M., Biochemistry and Molecular Biology Education 33 (1) (2005) 74–75. arXiv:arXiv:1011.1669v3, doi:10.1002/bmb.2005.494033010419.
URL http://doi.wiley.com/10.1002/bmb.2005.494033010419

[35] V. J. Voet, Donald, Biochemistry, no. 1, 2014. arXiv:arXiv:1011.1669v3, doi:10.1007/s13398-014-0173-7.2.

[36] R. H. Perry, D. W. Green, Perry's Chemical Engineers' Handbook, 8th Edition, McGraw-Hill Professional, 2008.

[37] R. Darby, Chemical engineering fluid mechanics, Marcel Dekker, New York, 2001.

[38] B. V. Kulkarni, R. D. Mattes, Lingual lipase activity in the orosensory detection of fat by humans, Am J Physiol Regul Integr Comp Physiol. 306 (12) (2014) 879–885. doi:10.1152/ajpregu.00352.2013.

[39] M. Alsahli, J. E. Gerich, Renal glucose metabolism in normal physiological conditions and in diabetes, Diabetes Research and Clinical Practice 33 (2017) 1–9. doi:10.1016/j.diabres.2017.07.033.

[40] C. Meyer, M. Stumvoll, J. Dostou, S. Welle, M. Haymond, J. Gerich, Renal substrate exchange and gluconeogenesis in normal postabsorptive humans., American journal of physiology. Endocrinology and metabolism 282 (2) (2001) E428–34. doi:10.1152/ajpendo.00116.2001.

[41] C. Meyer, J. M. Dostou, S. L. Welle, J. E. Gerich, J. M. Dostou, S. L. Welle, J. E. Gerich, Role of human liver , kidney , and skeletal muscle in postprandial glucose homeostasis, Am J Physiol Endocrinol Metab 282 (2002) 419–427.

[42] J. P. H. Wilding, The role of the kidneys in glucose homeostasis in type 2 diabetes: Clinical implications and therapeutic significance through sodium glucose co-transporter 2 inhibitors, Metabolism: Clinical and Experimental 63 (10) (2014) 1228–1237. doi:10.1016/j.metabol.2014.06.018.